

PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

PCT

To: VOSSIUS & PARTNER Siebertstrasse 4 D-81675 München GERMANY	EINGEGANGEN Vossius & Partner 17. Dez. 2004 Frist bearb.: 14.1. UF Ig
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Applicant's or agent's file reference H2216 PCT S3	<i>7.1. Dec 2004</i> PCT/EP2004/008114
International application No. PCT/EP2004/008114	
Applicant TRANSGENE S.A.	

INVITATION TO PAY ADDITIONAL FEES

(PCT Article 17(3)(a) and Rule 40.1)

REGISTERED MAIL

Date of mailing (day/month/year) 15/12/2004
PAYMENT DUE within 30 XXXX days from the above date of mailing
International filing date (day/month/year) 20/07/2004

1. This International Searching Authority

- (i) considers that there are 19 (number of) inventions claimed in the international application covered by the claims indicated ~~XXXX~~ on the extra sheet:

and it considers that the international application does not comply with the requirements of unity of invention (Rules 13.1, 13.2 and 13.3) for the reasons indicated ~~XXXX~~ on the extra sheet:

(ii) has carried out a partial international search (see Annex) will establish the international search report on those parts of the international application which relate to the invention first mentioned in claims Nos.:
see annex

(iii) will establish the international search report on the other parts of the international application only if, and to the extent to which, additional fees are paid

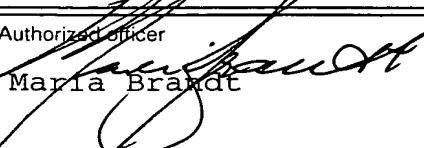
2. The applicant is hereby **invited**, within the time limit indicated above, to pay the amount indicated below:

EUR 1.550,00	x	18	= EUR 27.900,00
Fee per additional invention		number of additional inventions	total amount of additional fees

Or, _____ x _____ = _____

The applicant is informed that, according to Rule 40.2(c), the payment of any additional fee may be made under protest, i.e., a reasoned statement to the effect that the international application complies with the requirement of unity of invention or that the amount of the required additional fee is excessive.

3. Claim(s) Nos. _____ have been found to be unsearchable under Article 17(2)(b) because of defects under Article 17(2)(a) and therefore have not been included with any invention.

Name and mailing address of the International Searching Authority  European Patent Office, P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Authorized officer  Maria Brandt
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This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

Invention 1

claims 1-11,15-41 as far as they relate to any of the specific combinations of IL-2 with IL-7

Inventions 2-7

claims 1-11,15-41 as far as they relate to any of the specific combinations of IL-2 with any of IL-15, IL-18, IL-21, IL-27, IL-31, or IFNgamma

Invention 8

claims 1-11, and 15-41
as far as they relate to fusion proteins comprising IL-7

Invention 9

claims 1-11, and 15-41
as far as they relate to fusion proteins comprising IL-15

Invention 10

claims 1-41
as far as they relate to fusion proteins comprising IL-18

Invention 11

claims 1-11, and 15-41
as far as they relate to fusion proteins comprising IL-21

Invention 12

claims 1-11, and 15-41
as far as they relate to fusion proteins comprising IL-27

Invention 13

claims 1-11, and 15-41
as far as they relate to fusion proteins comprising IL-31

Inventions 14-19

claims 1-11,15-41 as far as they relate to any of the specific combinations of IFNgamma with
(8.1.) IL-15
(8.2.) IL-18
(8.3.) IL-21
(8.4.) IL-27
(8.5.) IL-31
(8.6.) IL-7

The present set of claims lacks unity within the meaning of R. 13.2. PCT.

The unifying concept of the application as filed is a fusion protein comprising two cytokines (claim 1). More specifically claimed are fusion proteins comprising any two of IL-2, IL-7, IL-15, IL-18, IL-21, IL-27, IL-31, and IFN-gamma (claim 7).

The cited prior art (EP158198, Rock et al., EP225579, EP288809, EP816510, WO94/21792) discloses several examples of fusion proteins composed of two different cytokines. In view of these documents, the concept of linking two cytokines as required by claim 1 is not new and therefore cannot provide the special technical concept or feature as required by R. 13.2 PCT.

The technical problem solved by the present application is the provision of further fusion proteins comprising cytokines. The solution are the fusion proteins as defined in the claims. In view of the cited prior art, these further fusion proteins are not linked by common special technical features.

Inventions 1-7 and 14-19, respectively are not linked by special technical features according to R. 13.2. PCT.
Fusion proteins with IL-2 have been known (e.g. IFNg-IL-2, IL-2 - IFNg, IL-2-GM-CSF, IL-2 - IL-6, and IL-2 - IL-2). Therefore, the group of inventions unified by the presence of IL-2 does not meet the requirements of R. 13.2 EPC, and each fusion protein based on IL-2 constitutes an individual invention. Likewise, because IFNg fusion proteins were already known, any further IFNg based fusion protein constitutes an independent invention.

In total there are 19 independent groups of inventions.

1. The present communication is an Annex to the invitation to pay additional fees (Form PCT/ISA/206). It shows the results of the international search established on the parts of the international application which relate to the invention first mentioned in claims Nos.:

see 'Invitation to pay additional fees'
2. This communication is not the international search report which will be established according to Article 18 and Rule 43.
3. If the applicant does not pay any additional search fees, the information appearing in this communication will be considered as the result of the international search and will be included as such in the international search report.
4. If the applicant pays additional fees, the international search report will contain both the information appearing in this communication and the results of the international search on other parts of the international application for which such fees will have been paid.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 158 198 A (TAKEDA CHEMICAL INDUSTRIES LTD) 16 October 1985 (1985-10-16) the whole document	✓ ✓ 1, 2, 5-7, 17-19, 29-31, 34-36
X	ROCK F ET AL: "OVEREXPRESSION AND STRUCTURE-FUNCTION ANALYSIS OF A BIOENGINEERED IL-2/IL-6 CHIMERIC LYMPHOKINE" PROTEIN ENGINEERING, OXFORD UNIVERSITY PRESS, SURREY, GB, vol. 5, no. 6, September 1992 (1992-09), pages 583-591, XP000983961 ISSN: 0269-2139 abstract	 ✓ ✓ 1, 2, 5-7, 17-19, 29-31, 34-36
X	EP 0 225 579 A (SEARLE & CO) 16 June 1987 (1987-06-16)	✓ ✓ 1, 2, 5-7, 17-19, 29-31, 34-36
X	page 8; claim 8	
X	EP 0 288 809 A (HOECHST AG) 2 November 1988 (1988-11-02) the whole document	✓ ✓ 1-5
		-/-

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

° Special categories of cited documents :

- °A° document defining the general state of the art which is not considered to be of particular relevance
- °E° earlier document but published on or after the international filing date
- °L° document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- °O° document referring to an oral disclosure, use, exhibition or other means
- °P° document published prior to the international filing date but later than the priority date claimed

- °T° later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- °X° document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- °Y° document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- °&° document member of the same patent family

Annex to Form PCT/ISA/206
COMMUNICATION RELATING TO THE RESULTS
OF THE PARTIAL INTERNATIONAL SEARCH

International Application No
PCT/EP2004/008114

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 816 510 A (TORAY RESEARCH CENTER INC ; TORAY INDUSTRIES (JP)) 7 January 1998 (1998-01-07) the whole document -----	✓ ✓ 1-5
X	WO 94/21792 A (VIAGENE INC) 29 September 1994 (1994-09-29)	✓ ✓ 1-9, 15-20, 22, 26-31, 34-36, 38,40 19-23
Y	pages 10,13,29; claims 1,9,11,17 -----	19-23
Y	WO 98/40498 A (SULLIVAN DANIEL M ; US ARMY (US); ANGLADE EDDY (US); CSAKY KARL G (US)) 17 September 1998 (1998-09-17) figure 1 -----	✓ ✓ 19-21
Y	WO 99/36440 A (HAWKINS ROBERT EDWARD ; UNIV BRISTOL (GB); WHITTINGTON HAYLEY ANN (GB)) 22 July 1999 (1999-07-22) claim 27 -----	✓ ✓ 19-21
Y	WO 98/08947 A (US HEALTH) 5 March 1998 (1998-03-05) ----- pages 16,19,44	✓ ✓ 1-11, 15-38, 40,41
Y	KAUFMANN A.M. ET AL: "Comparison of cytokines and CD80 for enhancement of immunogenicity of cervical cancer cells" IMMUNOBIOLOGY, vol. 202, no. 4, October 2000 (2000-10), pages 339-352, XP009040509 GERMANY abstract -----	✓ ✓ 1-9, 15-38, 40,41
Y	KONDO M ET AL.: "Enhancement of Interleukin-2 induced lymphokine-activated killer activity by Interleukin-7 against autologous human renal cell carcinoma" ONCOLOGY, vol. 55, no. 6, November 1998 (1998-11), pages 588-593, XP009040510 SWITZERLAND abstract -----	✓ ✓ 1-9, 15-38, 40,41
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Annex to Form PCT/ISA/206
COMMUNICATION RELATING TO THE RESULTS
OF THE PARTIAL INTERNATIONAL SEARCH

International Application No
PCT/EP2004/008114

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	JU D W ET AL: "Adenovirus-mediated combined suicide gene and interleukin-2 gene therapy for the treatment of established tumor and induction of antitumor immunity." JOURNAL OF CANCER RESEARCH AND CLINICAL ONCOLOGY. 1998, vol. 124, no. 12, 1998, pages 683-689, XP002307305 ISSN: 0171-5216 abstract ----- US 6 552 005 B1 (MILLER C RYAN ET AL) 22 April 2003 (2003-04-22) the whole document ----- WO 93/20849 A (UNIV TEXAS) 28 October 1993 (1993-10-28) cited in the application the whole document ----- WO 99/60128 A (LEMBACH KENNETH J ; SHANAFELT ARMEN B (US); JESMOK GARY (US); BAYER AG) 25 November 1999 (1999-11-25) cited in the application the whole document ----- SHANAFELT ARMEN B ET AL: "A T-cell-selective interleukin 2 mutein exhibits potent antitumor activity and is well tolerated in vivo" NATURE BIOTECHNOLOGY, vol. 18, no. 11, November 2000 (2000-11), pages 1197-1202, XP002307306 ISSN: 1087-0156 cited in the application the whole document -----	22,23 ✓ ✓ 23 ✓ ✓ 10,11 ✓ ✓ 10,11 ✓ ✓ 10,11

Patent Family Annex

Information on patent family members

International Application No PCT/EP2004/008114	
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Patent document cited in search report		Publication date		Patent family member(s)	Publication date
EP 0158198	A	16-10-1985	WO EP JP	8504420 A1 0158198 A1 60241890 A	10-10-1985 16-10-1985 30-11-1985
EP 0225579	A	16-06-1987	US AU AU CA DE DE EP JP JP JP JP JP JP JP JP US US ZA	4935233 A 599936 B2 6585186 A 1304024 C 3686397 D1 3686397 T2 0225579 A2 2752336 B2 7313170 A 2759074 B2 9118698 A 2612854 B2 62282593 A 5114711 A 6545124 B1 8609090 A	19-06-1990 02-08-1990 04-06-1987 23-06-1992 17-09-1992 17-12-1992 16-06-1987 18-05-1998 05-12-1995 28-05-1998 06-05-1997 21-05-1997 08-12-1987 19-05-1992 08-04-2003 24-02-1988
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EP 0816510	A	07-01-1998	EP CA WO	0816510 A1 2213512 A1 9723639 A1	07-01-1998 03-07-1997 03-07-1997
WO 9421792	A	29-09-1994	US AU CA EP JP WO US	5662896 A 6411994 A 2158546 A1 0689593 A1 9503740 T 9421792 A2 6310045 B1	02-09-1997 11-10-1994 29-09-1994 03-01-1996 15-04-1997 29-09-1994 30-10-2001

Patent Family Annex

Information on patent family members

International Application No

PCT/EP2004/008114

Patent document cited in search report		Publication date		Patent family member(s)	Publication date
WO 9840498	A	17-09-1998	US AU WO	5998598 A 6695398 A 9840498 A2	07-12-1999 29-09-1998 17-09-1998
WO 9936440	A	22-07-1999	AU EP WO	2173799 A 1066327 A2 9936440 A2	02-08-1999 10-01-2001 22-07-1999
WO 9808947	A	05-03-1998	AU WO	5507098 A 9808947 A1	19-03-1998 05-03-1998
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WO 9320849	A	28-10-1993	US AT AU CA DE DE EP JP WO	5229109 A 226086 T 4284393 A 2133831 A1 69332413 D1 69332413 T2 0673257 A1 7508714 T 9320849 A1	20-07-1993 15-11-2002 18-11-1993 28-10-1993 21-11-2002 26-06-2003 27-09-1995 28-09-1995 28-10-1993
WO 9960128	A	25-11-1999	AU AU BG BR CA CN EP HU JP NO NZ PL RU SI SK TR WO US	759697 B2 4078499 A 104929 A 9910504 A 2327349 A1 1309705 T 1076704 A1 0101948 A2 2002515247 T 20005762 A 508098 A 344407 A1 2235729 C2 20643 A 17242000 A3 200003354 T2 9960128 A1 2004175357 A1	17-04-2003 06-12-1999 28-09-2001 09-01-2001 25-11-1999 22-08-2001 21-02-2001 28-09-2001 28-05-2002 11-01-2001 26-09-2003 05-11-2001 10-09-2004 28-02-2002 10-07-2001 21-03-2001 25-11-1999 09-09-2004

Important Information

general

- the claims cannot be changed at this point in the procedure, the transmitted report is not the ISR (see Art. 19 PCT)
- non-payment does not lead to a loss of rights, a new procedure will be started on entry into the regional or national phase
- any payments have to be effected directly to this ISA (account details on separate sheets), payments to other entities will not be accepted
- in case of a total of more than 2 inventions found: when paying please specify exactly which claims should be searched
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payments under protest according to Rule 40 PCT:

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